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# BIOLOGICAL BULLETIN

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## THE CORRELATION BETWEEN THE CYCLIC CHANGES IN THE UTERUS AND THE OVARIES IN THE GUINEA-PIG.<sup>1</sup>

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In former papers we analyzed the production of the maternal placenta and of the experimental placenta; we followed the cyclic changes in the mammalian ovaries and partly analyzed the factors determining the first step in these changes, namely ovulation. In this paper we shall describe more in detail the cyclic changes in the uterine mucosa of the guinea-pig and correlate these changes with those in the ovaries. We shall analyze the effect of pregnancy, of the corpora lutea and other parts of the ovaries on those changes.

### I. THE CYCLIC CHANGES IN THE UTERUS OF GUINEA-PIGS IN WHICH COPULATION TAKES PLACE.

*At the period of heat and soon after copulation.*—In the uterus the surface epithelium and the gland ducts show high cylindrical epi-

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thelium and there can be seen several rows of surface epithelium. The gland fundi have much lower and smaller cells. The number of mitoses in these cells varies. They may be absent or almost absent. Often there are mitoses present in the gland ducts and sometimes in the surface epithelium. They are always absent in the gland fundi. The connective tissue under the epithelium is rather cellular and fibrils may be missing, or be little pronounced; in the deeper connective tissue they are more prominent. Mitoses are usually lacking in the connective tissue, but a few may be present especially near the epithelium of the surface of the gland ducts. Some mononuclear cells and also a few polynuclear leucocytes can be seen in the mucosa and may migrate through the surface epithelium, or collect in its neighborhood. The uterus is usually slightly papillary. There is no marked hyperemia in the mucosa, which, however, is somewhat edematous. Some gland fundi are cystically dilated, and partly filled with leucocytes, partly without leucocytes.

Within the first hour after copulation the uterine epithelium (of the surface as well as of the gland ducts) is high cylindrical; in the gland fundi we find lower cuboidal cells; inasmuch as the quantity of cytoplasm is relatively small in the gland fundi, the blue color predominates if the sections are stained with haematoxylin and eosin. The glands as a whole are small, straight and widely separated. Mitoses are more or less frequent in the surface epithelium and in that part of the glands in which the cells are high cylindrical, the mitoses are, however, more frequent in the glands. The connective tissue is rich in cells, the nuclei are somewhat larger, the tissue is in parts somewhat edematous, especially towards the surface; no mitoses are seen in the connective tissue. Some gland ducts are filled with polynuclear leucocytes; these are also present around glands; many glands, however, are free from polynuclears. Small mononuclear cells migrate through the surface epithelium. One hour after copulation the condition of the mucosa is almost the same as five minutes after copulation; the number of the mitoses in the surface epithelium has perhaps been somewhat decreased. The mucosa is quite edematous; a mitosis is seen in the connective tissue (perhaps in an endothelial cell.) Some spermatozoa are

visible in the lumen of the uterus and of the glands. Leucocytes migrate through the mucosa into the glands.

Three, four and five hours after copulation, the surface epithelium is high cylindrical. Polynuclear leucocytes migrate through the surface epithelium and may injure epithelial cells of the surface epithelium; vacuoles may appear in the surface epithelium. As the result of the injurious effects of the leucocytes, the surface epithelial cells may become lower and their nuclei deformed and contracted. There are not any, or only a few mitoses in the surface epithelium. The gland ducts are high cylindrical; they appear with hæmatoxylin-eosin red-stained, the cytoplasm preponderating. The ducts are short, the gland fundi have lower cuboidal epithelium. In the gland ducts there are some mitoses present; they are missing in the gland fundi where the cells are cuboidal. Polynuclear leucocytes migrate also through gland epithelium into the glands and may occasionally injure the gland epithelium. The connective tissue shows a distinct fibrillar character; its nuclei are rather large; it is somewhat edematous; some leucocytes migrate from the vessels through the connective tissue towards the epithelium. There are a few mitoses in endothelial cells of blood vessels and possibly also in connective tissue cells. The uterus shows blunt papillae. The sperm fluid present in the lumen of the uterus exerts a pressure on the surface epithelium and may thus contribute to the harmful influence of the leucocytes. In a specimen eight hours after copulation, the same results were obtained. There were, however, numerous mitoses in the surface epithelium.

It seems, therefore, as if the number of mitoses in the surface epithelium a few hours after copulation was determined by accidental conditions such as the action of leucocytes and pressure of the fluid, and was, therefore, variable to the same extent as these factors varied. The leucocytes may pass in such quantities through the mucosa into the lumen of the uterus that the fluid in the uterine cavity appears like an abscess and the leucocytes almost destroy the surface epithelium at certain places. Agglutinated spermatozoa are seen in the lumen of the uterus a few hours after copulation, and spermatozoa are also seen in the gland ducts. The polynuclear leucocytes migrate

in large numbers through the connective tissue of the mucosa, through the epithelium and the gland ducts. Under their influence much of the surface epithelium has been destroyed and even the epithelium of the gland ducts has been loosened.

Soon after parturition the guinea-pig is ready to copulate. At this time the mucosa is papillary and low. The muscle tissue lies at a number of places near the surface epithelium; the glands are therefore short; the epithelium is cuboidal or cylindrical, at some places high and with much cytoplasm; the vesicular nuclei are often at the base of the cell. Sometimes there are vacuoles in the epithelial cells. Mitoses are extremely rare in the epithelium; the gland cells are small and without mitoses. The connective tissue in the mucosa is somewhat edematous; it forms only a small layer; the nuclei are not large, rather densely packed; mitoses are not visible. At some places the epithelium is absent and coagulated blood with polynuclear leucocytes covers the surface. The muscle tissue is turgid and some plasmodia are visible around the vessels of the muscular coat. The condition of the surface epithelium is here apparently similar to the epithelium during the period of heat.

*From twelve to twenty-four hours after copulation.*—This period is marked through the great number of polynuclear leucocytes seen in the lumen of the uterus, in the lumen of the glands and especially in the upper ducts of the glands. There may be also present abscess-like collections of polynuclear leucocytes in the connective tissue of the mucosa. They may raise up the surface epithelium from the underlying connective tissue at some places; at other places they rarify and almost destroy the epithelial cells. We may still see twelve hours after copulation the high cylindrical shape of these cells. The glands are short and they do not show much branching; the gland ducts still show a lining of cylindrical cells; some gland-lumina are dilated through masses of leucocytes and the leucocytes may exert such a pressure on the walls of the glands that the epithelium becomes flat. Mitoses are seen at this period.

*From one to four days after copulation.*—Two days, five and a half hours, and two days, seven hours after copulation, the epithelium of the surface and of the gland ducts is cylindrical

and usually high; the gland fundi do not show as high an epithelium. There are mitoses present in the surface epithelium and in the upper and medium parts of the glands; but the mitoses may reach also further into the lower part of the glands. The gland fundi are not large nor separated from each other by much connective tissue. The connective tissue of the mucosa contains many nuclei; the fibrils are not pronounced and the tissue has a succulent, somewhat myxoid appearance; the nuclei are vesicular. Between the gland fundi the connective tissue is more fibrillar. No mitoses are as yet visible in the connective tissue of the mucosa; some leucocytes are still to be found there. We see, therefore, that the large masses of leucocytes have mostly disappeared as early as two days after copulation, and that the damage done to the epithelial structure has been repaired.

*In the first half of the fourth day after copulation* the epithelial structures are on the whole unchanged; the surface and gland duct epithelium is cylindrical, but at the surface there may be some cuboidal cells; the gland fundi are still composed of smaller cells, but in the second half of the day, the gland fundi also become active and show frequent mitoses. In the surface epithelium there are at this period either none at all, or only exceptional mitoses. At this period begins also the increase in the number of connective tissue cells in the mucosa. Three days, eight hours after copulation, the connective tissue of the mucosa has a myxoid character; the nuclei of the connective tissue cells are still small, but a little larger than at former periods; only exceptionally a mitosis is visible in the connective tissue of the mucosa. Many blood vessels are present and the tissue appears hyperemic, but no mitoses are seen in the vessels. The connective tissue between the fundi is denser. Three days and twelve hours after copulation, the mucosa is wider; there are round or oval vesicular nuclei present in the connective tissue cells; their cytoplasm is permeated with vacuoles; a certain though not yet large number of mitoses is seen in the connective tissue cells and these mitoses are independent of mitoses in endothelial cells of blood vessels which also occur. Thus the connective tissue cells become gradually transformed into predecidual cells. The connective tissue assumes a similar structure as regenerating

connective tissue in wounds, the vessels running at right angles to the bundles of connective tissue cells. The enlargement of the connective tissue causes a drawing out of the gland ducts and now mitoses appear also in the gland fundi, perhaps as a result of the pull exerted on the gland ducts. Some leucocytes migrate through the mucosa and epithelium.

*About four days after copulation*, or soon afterwards, the surface epithelium has become lower; it is either cuboidal or cylindrical, of medium height. No mitoses are present in the surface epithelium or in the cuboidal or low cylindrical gland ducts. The cells in the fundi of the glands are cylindrical and there are very many mitoses present. The mitoses migrate therefore gradually from the surface into the gland fundi, and concomitantly with the decrease in mitoses we find a decrease in the size and shape of the epithelial cells of the surface and gland ducts. In the connective tissue there is now a decided increase in the number of mitoses especially in cells near the surface and gland epithelium. The connective tissue cells themselves have vesicular nuclei and form fibrillar processes. Between the gland fundi the intercellular fibrils are more marked; the number of nuclei is smaller and there are less mitoses present. The tissue may, however, be edematous. The mitoses are mainly present in the fibroblasts, but there are some mitoses also in endothelial cells of capillaries. The proliferation takes place principally in the fibroblasts and the predecidual cells do not originate in the endothelium of the blood vessels. The vessels are often running directly towards the surface epithelium and at right angles to the direction of the connective tissue cells. There are occasionally some polynuclears present in alveoli of glands.

*Six to eight days after copulation*.—Six days, and on the seventh day after copulation, the surface and the gland epithelium is cuboidal low, or medium cylindrical. The gland ducts are drawn out. In the glands there may still be some higher cylindrical epithelial cells left; nowhere are mitoses present in the epithelium. There are mitoses in the connective tissue underneath the surface epithelium and between the gland ducts. The arrangement is the one typical for regenerating connective tissue, the vessels running at right angles to the layers of the

connective tissue. Below the epithelium there are layers of densely packed large vesicular nuclei; the cells are often free, not enveloped by fibrils. The number of mitoses varies somewhat at different places. The gland fundi are surrounded by edematous connective tissue and between the gland fundi we find fibrillar connective tissue. The cellular connective tissue separates the gland fundi from the surface epithelium. Some polynuclear leucocytes are in the mucosa; we see here some disintegrating cells; it is possible that they are mainly polynuclear leucocytes.

Seven days, and on the first half of the eighth day after copulation, the surface epithelium is cuboidal or low-medium cylindrical; at a few places it is somewhat higher with vacuoles in the outer part of the cells; the nuclei are small vesicular. Usually no mitoses are present, but in one piece a few mitoses could be seen.

The epithelium of the glands is cuboidal or low cylindrical; the glands are drawn out. In one piece there are still a number of mitoses in the gland fundi, although the gland cells are here cuboidal. The structure of the connective tissue is similar to that of the previous period. There are mitoses present in the cell layer but they are not quite as frequent as before. The cell layer consists of round, relatively small cells with many capillaries with narrow endothelium. There is some hyperemia present. At other places the nuclei in the cell layer are round vesicular, and the cytoplasm of the neighboring cells is connected by bridges.

Eight days, eight hours, after copulation, the structure of the surface epithelium and glands is similar to the previous period. The epithelial cells are low. No mitoses are present. The glands are not very large and contain a relatively small number of coils. There is still some cell layer present under the surface epithelium; the vesicular nuclei are compressed and a number of nuclei under the epithelium disintegrate, perhaps the nuclei of the proliferated connective tissue layer.

*Eight to seventeen days after copulation.*—In order to prevent pregnancy the tubes had been ligatured near the junction with the uterus soon after copulation.



*Ten to eleven days after copulation.*—The surface epithelium is lower than at the beginning of the sexual cycle; it is cuboidal or low cylindrical; at certain places there may be swollen cells. There are generally no vacuoles in the epithelium; mitoses are usually missing; they were present only in one place. The glands are small coiled, lying near the surface, are without a wide lumen, their cells are not high and without mitoses. The connective tissue of the mucosa is well supplied with capillaries, which run at right angles to rows of connective tissue cells. The connective tissue is still partly myxoid under the surface of the epithelium. At some places there are still many vesicular nuclei densely packed. In the deeper connective tissue between the coils of the glands there are smaller nuclei and some fibrils. Only one mitosis is seen in a connective tissue cell in the mucosa. There is some nuclear debris present under the epithelium; some mononuclears are in the mucosa tending to migrate through the epithelium.

*Twelve to fourteen days after copulation.*—Low cuboidal or low cylindrical epithelium of surface with *frequent* mitoses, especially at places of invagination of the epithelium; glands with low cuboidal or low cylindrical epithelium without mitoses. In the connective tissue there are no mitoses; small vesicular nuclei of connective tissue cells under the epithelium of the surface. The further the connective tissue is removed from the surface epithelium, the more the fibrils become developed and the smaller the nuclei. There is occasionally a little edema in the connective tissue. Some small mononuclear cells may migrate through the epithelium. The layer of proliferated connective tissue cells which was previously present is much smaller now than five to seven days after ovulation. The glands are correspondingly smaller. At this period mitoses appear again in the surface epithelium.

*Fifteen to seventeen days after copulation.*—The epithelial cells are low cuboidal; mitoses are present only in the surface epithelium. The connective tissue contains small nuclei and is fibrillar. Near the surface epithelium the nuclei are relatively more frequent and vesicular in the connective tissue, and the fibrils are less developed than in the deeper parts of the mucosa.

Occasionally some edema is present in the surface epithelium and at such places vacuoles are present in the epithelial cells.

This condition of the uterus may exist notwithstanding the presence of follicles in the ovaries which are near maturity. The latter do, therefore, at least as long as the corpora lutea functionate, not produce the changes in the mucosa of the uterus which are characteristic of the first period in the sexual cycle.

*During pregnancy* the uterus below or above the insertion of the placenta or in the horn in which there happens to be no embryo shows low cuboidal or low cylindrical epithelium with or without mitoses. There may be some vacuoles in the epithelial cells. There are small narrow coiled glands with low cylindrical epithelium. There is no large connective tissue cell layer present. The nuclei in the connective tissue of the mucosa are small and surrounded by well developed connective tissue fibrils; especially between the gland fundi do we find large connective tissue fibers, while underneath the epithelium the number of connective tissue nuclei is relatively greater and the tissue is less fibrillar. Mitoses occur neither in the glands nor in the connective tissue. It seems that in the earliest stages of pregnancy less than ten days after copulation, there are not any or only exceptional mitoses in the surface epithelium; correspondingly we saw previously that six to ten days after a previous period of heat—copulation having been prevented—no mitoses were found in the surface epithelium. During the middle or end of pregnancy the uterine mucosa has a similar structure; but there may be present some papillæ in the mucosa. The presence of mature, or nearly mature follicles in the ovaries is without influence on the structure of the uterus during pregnancy.

## II. THE SEXUAL CYCLE OF UTERUS AND OVARIES IN GUINEA-PIGS IN WHICH HEAT HAD BEEN OBSERVED BUT COPULATION PREVENTED, IS AS FOLLOWS:

*At the period of heat previous to the rupture of the follicles* we find the following condition: In the ovaries we find one or more small corpora lutea which are just beginning to degenerate (vacuolization in the periphery). The follicles with exception of the smallest show degeneration of the granulosa. There may

be at earlier stages still some good medium-sized follicles. There are present one or several mature follicles usually with maturation spindle in the ovum of the follicle. Other follicles show early and medium stages of connective tissue atresia. There are usually many follicles in or near the last stage of connective tissue atresia, but the number of such follicles varies and may be relatively small in very young ovaries at the time of the first heat. The structure of the uterus at this period has been described above (see page 1). It is identical with the structure of the uterus in the period of heat when the latter is followed by copulation. Even after extirpation two months previously of the greater part of the uterus, the same phenomena can be observed; heat takes place and mature follicles form. The remaining small part of the uterus forms a little cyst with cylindrical (or cuboidal) epithelium with many mitoses. The gland ducts have highly cylindrical epithelium and also show mitoses. This has been observed in two experiments. Also after almost complete extirpation of the thyroid one to two months previously, heat occurs accompanied by the typical changes in the uterus and ovaries. The small remaining part of the thyroid may consist of acini with cylindrical epithelium while the colloid may be almost, or entirely absent.

At a slightly later period, namely, soon after the rupture of the mature follicles, the condition of the ovaries and uterus is essentially the same; two changes have however, taken place, namely (1) the surface epithelium is not quite so regularly high cylindrical, but may be at certain parts cuboidal; and (2) we find more or less pronounced changes in the surface epithelium and sometimes in the adjoining part of the gland ducts, namely, vacuolization in the epithelial cells; in the vacuoles which press upon the nuclei we may find degenerating cells; chromatin particles may spread over the greater part of the cells. These changes are probably due to the immigration of mononuclear cells or polynuclear leucocytes from the mucosa into the epithelium. Here these immigrated cells degenerate. One sees sometimes mononuclear cells immigrating into the epithelium. It is not very probable that the changes in the epithelium following ovulation are brought about through a disintegration of some epithelial cells.

Mitoses are very rare in the epithelial structures; there may be however a very small number present in the surface epithelium or in the upper gland ducts. Some glands at this period are dilated and filled with polynuclears. Only rarely do we see a mitosis in the connective tissue. We find in some pieces soon after the rupture of the mature follicles hemorrhages beneath the epithelium which may raise the surface layer of the epithelium from the underlying connective tissue.

The same condition we find also in the course of the first day after the rupture of the follicles, at a time, therefore, when connective tissue begins to grow into the follicular cavity. Perhaps the degenerative changes in the surface epithelium are even more marked at this period.

In four animals in which the ovaries and uterus were examined seventeen and eighteen days after a previous heat, we found ruptured follicles in the animals examined (after seventeen days) or very young corpora lutea (after eighteen days) and the corresponding condition of the uterine mucosa.

We may therefore conclude that in animals kept under normal conditions the period of heat occurs approximately every fifteen to nineteen days, a conclusion that is corroborated by other observations which we made. We furthermore conclude that the condition of the uterine surface epithelium indicates in most cases whether or not a rupture of a follicle has taken place in the ovary.

In a specimen obtained *about one to one-and-a-half days after spontaneous ovulation*, in which no copulation had taken place, there were present at most places high cylindrical epithelium of the surface; at some places, however, the epithelium was somewhat lower; gland fundi show as usual lower epithelium. In the surface epithelium and in the gland ducts with higher epithelium there are mitoses present. The mucosa is rich in cells; is partly a little edematous; there is no increase in the size of the mucosa visible and no mitoses are seen. Some polynuclear leucocytes are present in the mucosa, connective tissue as well as glands, although no spermatozoa had entered the uterus; but the number of leucocytes is much smaller than in cases in which copulation had taken place.

*Three days after heat* we find a vacuolar corpus luteum of the former period, in process of degeneration. In the central cavity of the new corpora lutea new connective tissue is present in the periphery. There are many small, and small to medium-sized good follicles; many follicles in an early-medium stage of connective tissue atresia, and a large number of follicles in the late stages of connective tissue atresia.

The surface epithelium of the uterus is mostly high cylindrical, but may be at places cuboidal, probably as a result of stretching. It does not show any longer the changes observed in the first two days after ovulation. It is usually free from mitoses; the gland duct epithelium is high cylindrical and the epithelium of some fundi begins to become also higher. There are many mitoses present in the gland ducts, especially in their medium parts; the mitoses begin now to proceed further downwards and occasionally may be found in these gland fundi which have enlarged. The connective tissue of the mucosa is, especially in the higher parts, rather cellular, with vesicular nuclei, but without mitoses; it may be somewhat myxoid.

In the mucosa we find some small mononuclear cells and also some polynuclear leucocytes. Some mononuclears may immigrate into the gland and surface epithelium. There may be seen some cystically dilated glands.

*Four days after heat* the corpus luteum of the former period is vacuolar; the new follicles are well developed. There are many small and medium-sized good follicles, and many follicles in medium or the last stage of connective tissue atresia. The epithelium of the surface and gland ducts is no longer as high as before; it is cylindrical, of medium height, or cuboidal-cylindrical; the epithelium of the gland fundi is higher than before. There are many mitoses present in the gland fundi; but nowhere else in the epithelium. Some glands are dilated and contain polynuclear leucocytes. The connective tissue layer under the epithelium is enlarged and shows frequent mitoses. The uterus is slightly papillomatous and in the connective tissue of the papillæ there is some edema. The epithelium over the edematous connective tissue may also be edematous.

*Five days after heat*, we find in the ovaries many small and

medium-sized good follicles, a number of follicles in a medium stage of connective tissue atresia, and there are a large number of follicles in the last stage of connective tissue atresia. The surface and glandular epithelium is cylindrical, of medium height and is almost without mitoses; a few isolated mitoses may be found in the gland fundi. The cell layer of the connective tissue contains many mitoses; there are some small mononuclear, and a few polynuclear leucocytes in the mucosa.

*Six days after heat*, the corpora lutea of the former period are quite vacuolar and in process of degeneration. There are good new corpora lutea and many good small, medium-sized and large follicles, and many follicles in the last stages of connective tissue atresia. The surface epithelium of the uterus is cylindrical and of medium height; the epithelium of the gland ducts and gland fundi is cuboidal-cylindrical. There are nowhere mitoses present in the epithelium. There are mitoses present in the connective tissue cell layer of the mucosa, but the mitoses are here probably not as frequent as at five days after the previous period of heat. There are many small mononuclear cells in the connective tissue.

*Seven days after heat*, we find good corpora lutea, many good small medium-sized and large follicles, no follicles with granulosa degeneration and many follicles in the last stage of connective tissue atresia. The epithelium of the surface and glands of the uterine mucosa is cuboidal or cylindrical of medium height. No mitoses are present in the epithelium; some mononuclears can be found in the surface epithelium. In the connective tissue cell layer there are a number of mitoses, but not as many as five days after heat. Some polynuclear leucocytes and small mononuclear cells are in the mucosa and some nuclei disintegrate in the upper layer of the connective tissue.

*Eight days after heat*, the condition of the ovaries is the same as seven days after the period of heat, but degeneration of the granulosa has now set in in some of the larger follicles. The corpora lutea of the former period are quite vacuolar and are in full process of retrogression. The epithelium of surface and glands of the uterus is cuboidal or cylindrical of medium height, without mitoses. In the connective tissue of the mucosa we still see blood vessels running towards the surface and at right

angles to the long axis of the connective tissue cells; but mitoses are no longer present and some cells disintegrate in the upper part of the mucosa.

*Nine days after heat.*—There is as yet not any, or very little granulosa degeneration in the large follicles; occasionally there may be more extensive degeneration of the granulosa and a few exceptional follicles may show an early stage of connective tissue atresia; in some ovaries all the large follicles are still well preserved. The follicles which six to eight days after the former period of heat were in the last stage of connective tissue atresia, shrink under the influence of the pressure of the growing follicles and corpora lutea.

The uterine epithelium of the surface is low to medium-sized cylindrical, a few vacuoles may be present in the epithelium, the gland epithelium is low cylindrical. The connective tissue of the mucosa shows still vesicular nuclei and vacuoles in the cells, but it is being somewhat compressed. There are no mitoses present in the epithelium or in the connective tissue.

*Eleven days after heat.*—We find good small, medium-sized and large follicles, some large follicles show granulosa degeneration or connective tissue in growth. The follicles which were formerly in the last stage of connective tissue atresia begin to disappear more and more; there are still the remains of the membranæ pellucidæ, surrounded by some very small compressed nuclei. The corpora lutea are in a good condition. Mature follicles appear again in the ovaries.

The epithelium of surface and gland ducts of the uterus is cylindrical, of medium size. The gland fundi are smaller. No mitoses are seen; some mononuclear cells may be present, but neither vacuoles nor chromatin particles; there is still some remnant of the cell layer in the mucosa, but it is becoming smaller and more fibrillar; only an exceptional mitosis can be found in the connective tissue.

*We find, therefore, active cell proliferation in the connective tissue of the mucosa from the fourth to the seventh day after the last ovulation. Approximately five days after ovulation the mitoses disappear also in the gland fundi. From the sixth to the twelfth day after ovulation, the epithelium of the uterine mucosa is without mitoses. Then they begin to reappear.*

*Twelve days after heat.*—There are many good small, medium-sized and large follicles; some large follicles show granulosa degeneration. A number of follicles show early and medium and some advanced connective tissue atresia. The follicles which had arrived about six to seven days after copulation at the last stage of connective tissue atresia are disappearing more and more. Some mature follicles may be present.

The surface and glandular epithelium of the uterus is cuboidal-cylindrical; some small mononuclear cells migrate through the surface epithelium. No definite mitoses can be seen in the surface epithelium. A few isolated gland ducts and the adjoining surface epithelium have high cylindrical epithelium. The mucosa is narrow and the nuclei of the connective tissue are small.

*Fourteen days after heat.*—In the corpora lutea some vacuolization begins in the periphery. There are good, small medium-sized and large good follicles, some large follicles show granulosa degeneration; other follicles are in the early or medium or a later stage of connective tissue atresia. These follicles which are now constantly degenerating all contribute to the follicles in the late stages of connective tissue atresia which we find at the time of heat.

The surface and gland duct epithelium of the uterus is cuboidal or cylindrical of medium height. The gland fundi are smaller. There are some mitoses present in the surface and gland duct epithelium. The mucosa is low, the connective tissue nuclei are small. There is some edema present in the connective tissue which may even raise up the surface epithelium. There may be some dilated glands with polynuclear leucocytes and some mononuclears in the mucosa.

*Fifteen days after heat.*—At this time the ovaries are about the same as fourteen days after heat. There are good small, medium-sized and large follicles; a number of large follicles show granulosa degeneration. A certain number of follicles are in the medium- or medium-late stages of connective tissue atresia. There are not many follicles in the last stage of connective tissue atresia. The follicles which degenerated at the period of the last heat have almost disappeared and the other degenerating follicles



have not yet advanced to the last stage of atresia. There are mature follicles present. The periphery of the corpora lutea show some slight vacuolization. The connective tissue of the uterine mucosa is at this period very edematous, the edematous fluid may raise the surface epithelium. The connective tissue nuclei are very small. The mucosa and also the muscularis of the uterus are thin. The epithelium of the surface and of the gland ducts is low cuboidal or low cylindrical. This is perhaps partly due to the pressure of the underlying edematous fluid. Where the connective tissue is very edematous, the overlying epithelial cells may also be somewhat edematous and vacuolar. At some places the epithelium of the surface and gland ducts is somewhat higher. Some mitoses are present in epithelial cells of the surface and at the entrance of the gland ducts. Exceptionally a mitosis may be found in a gland duct.

We see, therefore, that from the fourteenth day on, mitoses reappear in the surface epithelium of the uterine mucosa. If we compare the cyclic changes in the uterus in cases in which copulation took place and in which only the heat was observed, but copulation had been prevented, we find the following:

A few hours after copulation, the leucocytes begin to migrate in large numbers from the connective tissue of the mucosa through the surface epithelium into the lumen of the uterus. Here they collect in such large numbers eight hours after copulation that its contents may be like an abscess.

These leucocytes exert an injurious influence on the surface epithelium which is therefore after copulation very much earlier and very much more strongly injured than if copulation has been prevented. The epithelium of the gland ducts may also suffer. We find, a few hours after copulation, spermatozoa which may be agglutinated in the lumen of the uterus and also in the gland lumen. The same large number of polynuclear leucocytes is still present during the first twenty-four hours after copulation; they have however mostly disappeared two days after copulation. At that time the condition of the uterus is very similar in animals in which copulation took place and in which copulation had been prevented. A few leucocytes can also be seen in the uterus of animals in which copulation had been prevented. In such

animals also some degenerative changes occur in the uterine epithelium, but they are less marked than in animals which had copulated. An examination of the uterus permits us in most cases to determine whether or not ovulation had taken place at the time of the examination in a guinea-pig in which copulation had been prevented.

From now on, the condition of the uterus is similar in both series of guinea-pigs; the mitoses migrate from the surface epithelium to the gland fundi and disappear completely in the epithelium five to six days after the ovulation. The connective tissue proliferation starts on the fourth day and ceases seven days after ovulation. On the eighth day we find a beginning disintegration of cells in the upper part of the connective tissue of the mucosa. The later stages were also examined in the first series in animals in which after copulation, pregnancy had been prevented through an early ligature of the tubes. From the sixth to the twelfth day after ovulation the epithelium is without mitoses; they then begin to reappear in the surface epithelium. Notwithstanding the presence of mature follicles, the uterus does not assume the characteristic features of the uterus during heat. These changes occur only after signs of degeneration have begun to set in the corpora lutea.

During pregnancy the uterine epithelium is relatively low, mitoses occur only in the surface epithelium. The connective tissue layer is thin and no mitoses are found in the connective tissue cells. The uterus is therefore in a resting condition during pregnancy.

### III. THE EFFECT OF EXTIRPATION OF THE CORPORA LUTEA ON THE CYCLIC CHANGES IN THE UTERUS.

In a previous communication we have shown that extirpation of the corpora lutea within the first week after ovulation leads in the majority of cases to an acceleration of the next ovulation. In nine cases in which pregnancy was not present at the time of the examination, the ovulation had not yet taken place notwithstanding the complete extirpation of the corpora lutea. In four of these cases the uterus had been split within the first week after ovulation. In another case abortion had taken place

at the time of the examination; in the sixth case the guinea-pig had been in a very weak condition and in the ovaries no good large or mature follicles, but some large follicles in granulosa degeneration, were found. In the seventh case the corpora lutea had been burnt instead of excised with the scissors. As we saw previously, the burning out of the corpora lutea injures the ovaries and prevents in many cases an early ovulation. In four cases in which the uterus had been cut, and in one other case, one ovary had been excised previously.

The uterus in these cases in which ovulation had not been hastened through extirpation of the corpora lutea was found to be as follows:

(1) No. 642. Three days after copulation extirpate corpora lutea examination. Sixteen days after the previous copulation the animal was in a weak condition. In the ovaries there was no good large or mature follicle, there were some large follicles with granulosa degeneration. The surface epithelium of the uterus was cuboidal; it contained some vacuoles with chromatin particles; there were very few mitoses present. The uterine glands were cuboidal to cylindrical and showed no mitoses. The connective tissue was fibrillar, the nuclei near the surface epithelium were more numerous; no mitoses were present in the connective tissue.

(2) No. 693. Seven days after the previous copulation extirpate the corpora lutea; ten days later examination. Abortion had taken place. The ovaries showed small and large good follicles and large follicles with granulosa degeneration; mature follicles were present. There were also follicles in various stages of connective tissue atresia.

The surface epithelium of the uterus was cuboidal to cylindrical and showed many mitoses; the glands were small and without mitoses; there was fibrillar connective tissue; where abortion had taken place, the connective tissue was hyperæmic, edematous and there were many polynuclears in the vessels.

(4) No. 300. Twenty-three hours after copulation extirpate left ovary; six days later make incision into the uterus; seventeen days after copulation, examine the uterus. In the remaining ovary of the animal which was about four months old, no corpus luteum and only small and small-medium sized good follicles

were found, besides follicles in an early and medium stage of connective tissue atresia. The uterus shows low cylindrical epithelium and glands with similar epithelium; some glands are dilated. There is a very small number of mitoses in the surface epithelium and in the superficial part of the gland ducts; the connective tissue is fibrillar.

The uterus is similar in No. 270 (four days after copulation excise left ovary, three days later cut out the uterus, examination seventeen days after copulation). In the ovary there was no mature follicle. The epithelium of surface and glands of the uterine mucosa was low, mitoses only present in the surface epithelium; the connective tissue of the mucosa was fibrillar and with small nuclei, without mitoses.

Similar were the findings also in No. 93 (three and a half days after copulation extirpate left ovary, one day later make incision in the uterus, examination fourteen and one half days after copulation). In this case there is however at some places somewhat higher surface and gland epithelium. In No. 992 (six days, ten hours after copulation one ovary was extirpated; the uterus was not cut; eighteen days ten hours after the previous ovulation, the examination was made). In this case the uterine epithelium was low cuboidal to cylindrical and contained mitoses; the glands were similar without mitoses, the connective tissue underneath the epithelium had some larger vesicular nuclei, and became fibrillar somewhat deeper.

In No. 843 the corpora lutea had been extirpated six days, sixteen hours after copulation; ovaries and uterus examined twenty and one half days after ovulation; there were many good medium-sized follicles present, others showed granulose degeneration, still other follicles were in various stages of connective tissue atresia. The surface epithelium was cylindrical, of medium size. The gland duct epithelium was similar. There were frequent mitoses present in both; the connective tissue is fibrillar. At one place the uterus had been thickened. Here the connective tissue was somewhat edematous, the connective tissue nuclei were small; there was a mitosis present in a connective tissue cell at this place. In this case abortion had probably taken place at the thickened place. In No. 105 corpora lutea had been

burnt three days, twenty hours after copulation; twenty and one half hours later incisions were made into the uterus and fourteen days, seventeen hours after copulation, ovaries and uterus were examined. There were mature follicles present in the otherwise typical ovaries. The uterus was similar as in No. 270. The uterus was also similar in No. 391, where two days, seven hours after ovulation, the right ovary had been excised and one corpus luteum of the left ovary. Five days later the uterus had been incised and seventeen days after the last copulation ovaries and uterus were examined. No mature follicles were found in the ovaries.

In one case (No. 687) the corpora lutea had been extirpated seven days, seven hours after copulation and ten days later the uterus and ovaries were examined. In the uterus two pregnancies were found; the mucosa of the uterus above and below the decidua was poor in nuclei and fibrillar. In the ovaries there were mature follicles, but no new ovulation had as yet taken place.

We may conclude that in cases in which after an early extirpation of the corpora lutea no new ovulation takes place, the condition of the uterus does not undergo any marked changes.

As we stated previously in the majority of cases in which within the first week after ovulation the corpora lutea had been cut out with scissors a new ovulation takes place between the eleventh and sixteenth day after ovulation. If we examine the uterus in these animals we find the typical structure which we might expect in accordance with the time since the last ovulation.

(1) No. 669. Forty-nine hours after last copulation, extirpation of the corpora lutea. Examination of the ovaries and uterus twenty days after the last copulation. Examination of the ovaries revealed that an ovulation had taken place about seven to eight days previously; correspondingly we find in the uterus the typical condition: rather low cylindrical surface epithelium, small glands with the same epithelium, in the connective tissue of the mucosa small vesicular nuclei, pressed together; mitoses are lacking in epithelial as well as connective tissue cells.

(2) No. 772. Two days, seventeen hours after last copulation extirpate corpora lutea; examine uterus and ovaries not quite

eighteen days after copulation. Four to five days before the examination a new ovulation had taken place. The epithelium of the surface was found cylindrical of medium height without mitoses; the glands had the same epithelium; there were mitoses present in the fundi of the glands. The connective tissue of the mucosa showed a layer of vesicular nuclei; it has a somewhat myxoid character and contained many mitoses. This condition of the uterus was in accordance with the time of the last ovulation.

(3) No. 773. Two days, eight hours after copulation, extirpate the corpora lutea; sixteen days later examine uterus and ovaries. Ovulation had taken place about seven days previously. Surface epithelium and glands of uterus show cuboidal or cylindrical epithelium of medium height; there are no mitoses present. In the connective tissue there are still a large number of proliferated cells, but only one mitosis is visible in the connective tissue under the epithelium. This corresponds to the picture of the uterus about seven to eight days after copulation.

(4) No. 779. Six days after copulation extirpate corpora lutea. Twelve days later examine uterus and ovaries. The ovaries show that rupture had taken place about four days previously. Surface epithelium and gland cells are cylindrical, relatively high, there are many mitoses in the gland fundi; they are lacking elsewhere in the epithelium. Small mononuclear cells migrate through the epithelium; the connective tissue cells are swollen and are densest under the surface epithelium; they form a distinct cell-layer; there are mitoses in these connective tissue cells.

(5) No. 785. Six days, seventeen hours after copulation, extirpate corpora lutea; twelve days later examine uterus and ovaries. The ovaries show that a new ovulation had taken place five to six days previously. There was a cuboidal-cylindrical surface epithelium of the uterus without mitoses. The epithelium of the glands was somewhat higher and also without mitoses. There is a cellular connective tissue under the epithelium with mitoses; underneath the epithelium the nuclei are more densely packed; somewhat further down the tissue is more edematous. The glands and vessels run at right angles to the connective tissue layer.

(6) No. 755. One day, nineteen hours after copulation, left uterus ligatured; extirpate one corpus luteum in left ovary; six days later extirpate one corpus luteum of the right ovary. Examination of ovaries and uterus eighteen days after copulation. Pregnancy was not present. A new ovulation had taken place approximately two days previously, to judge from the condition of the ovaries. The uterus showed high cylindrical epithelium of the surface and of the gland ducts; in both many mitoses were present; some polynuclear leucocytes are in the lumen of some glands. In the connective tissue there are small nuclei present without mitoses. Some cells migrate through the surface epithelium.

We see in these as well as in other similar cases which we need not mention here, a parallelism between the condition of the ovaries and the uterus. An experimentally accelerated ovulation leads to the onset of a new cycle in the uterine mucosa.

#### IV. THE UTERUS OF PREGNANT GUINEA-PIGS IN WHICH AFTER EXCISION OF THE CORPORA LUTEA A NEW OVULATION HAD TAKEN PLACE.

As we stated in former papers during pregnancy no new ovulation takes place in the ovary of the guinea-pig.<sup>1</sup> However, after excision of the corpora lutea within the first week after copulation in a considerable number of cases, a new ovulation takes place notwithstanding the presence of pregnancy.<sup>2</sup> We saw that if in a non-pregnant guinea-pig an accelerated ovulation takes place after an early extirpation of the corpora lutea, the uterine mucosa undergoes the typical changes characteristic of the stage of the sexual cycle at which the examination had been made. It is different, if a new ovulation takes place in pregnant guinea-pigs, as the following observations demonstrate:

(1) No. 748. Twenty-one hours after copulation ligature and cut left tube at juncture with uterus, cut out one corpus luteum in the left ovary. Seven days after copulation, cut out one corpus

<sup>1</sup> "The Cyclic Changes in the Uterus of the Guinea-Pig," *Journal of Morphology*, Vol. 22, p. 37, 1911; *Virchows Arch.*, Vol. 206, 1911.

<sup>2</sup> *Deutsche Med. Wochenschrift*, 1911, No. 1.

luteum of the right ovary. Examination eighteen days after previous copulation shows the presence of embryo and placenta in the right horn of the uterus.

In the left ovary we found young corpora lutea in which a part of the central cavity was still present, while its periphery had been filled by connective tissue; there were small and small to medium-sized good follicles and many follicles in connective tissue atresia. Both uteri show low cuboidal cylindrical epithelium of the surface with vacuoles and narrow glands. The surface epithelium and occasionally the gland ducts near the surface contain some mitoses. The rest of the glands and the connective tissue are without mitoses. The connective tissue is fibrillar and without a cell-layer. Ovulation had taken place approximately three to four days previous to examination (fourteen to fifteen days after copulation). The uterus is typical for pregnancy, but does not show the usual cyclic changes.

(2) No. 752. Ligature left tube near junction with uterus, cut out one corpus luteum from left ovary thirty-three hours after copulation. Seven days after copulation cut out two corpora lutea from the right ovary; examined eighteen days after copulation; pregnancy in right horn of uterus. In the left ovary there were three new corpora lutea, in which the central cavity had been filled by connective tissue; one of the corpora lutea contained a retained ovum in the central cavity; there were small and medium-sized good follicles and various follicles in connective tissue atresia; many follicles were in the last stage of connective tissue atresia. There were some atretic yellow bodies, the remnants of former corpora lutea. The right ovary is similar. A new ovulation had taken place about four to five days previously (thirteen to fourteen days after previous copulation). In the uterus the cyclic changes are absent: we see low cuboidal or low cylindrical surface epithelium with vacuoles which contain chromatin particles and a number of mitoses, narrow glands without mitoses and fibrillar connective tissue rich in nuclei without mitoses. No cell-layer had been formed. The structure of the uterus is the same on the pregnant and non-pregnant side.

(3) No. 780. Six days, six hours after copulation, extirpate



two corpora lutea in left, one corpus luteum in right ovary. Examination ten days later showed the presence of one pregnancy in each horn. The ovaries contained good small and almost medium-sized follicles. There was present one small to medium-sized follicle with a partial, slowly progressing degeneration of the granulosa; there are, furthermore, follicles in various stages of connective tissue atresia. In the right ovary there are two young corpora lutea in which one half to two thirds of the central cavity had been filled by connective tissue. Ovulation had taken place four to five days previously (eleven to twelve days after the previous copulation). The uterus showed low cuboidal epithelium with vacuoles and some mitoses, small glands without mitoses. The connective tissue is fibrillar and contains small nuclei; no mitoses are present in the connective tissue. Cyclic changes in the uterus are absent; the uterus is characteristic of a pregnant guinea-pig.

(4) No. 781. Seven days, five and one half hours, extirpate two corpora lutea in right, one corpus luteum in left ovary. Examination eleven days later; two pregnancies in right horn of uterus; no pregnancy in left horn. In both ovaries there were new corpora lutea in which the central cavity had been filled with connective tissue. The condition of the ovaries indicated a new ovulation about four to five days previously (thirteen to fourteen days after copulation). The uterus shows the same condition as in the former animals (Nos. 748, 752, 780). The epithelium was low, the surface epithelium contained mitoses. The connective tissue did not contain a cell-layer and was without mitoses.

(5) No. 786. Seven days, five hours after copulation, extirpate one corpus luteum in each ovary. Nine days later examination showed one pregnancy in the right horn of the uterus. In both ovaries there were young corpora lutea in which connective tissue began to grow in the periphery of the central cavity; there were small good follicles and follicles in early-medium and late connective tissue atresia. Ovulation had taken place approximately two days previously (fourteen days after copulation). The uterus showed the same structure as in the previous specimens; but the surface epithelium did not contain

mitoses. Vacuoles were however present in small cuboidal cylindrical cells.

(6) No. 789. Seven days, twelve and a half hours after copulation extirpate two corpora lutea in right, one corpus luteum in left ovary. Examination ten days later shows one pregnancy in right, none in left horn. Both ovaries showed young corpora lutea in which the central cavity had been partly or entirely filled by connective tissue. In one of the young corpora lutea an ovum had been retained. There were small and medium-sized good follicles and many follicles in connective tissue atresia. Ovulation had taken place about four to five days previously, about thirteen days after the copulation. The left uterus showed cuboidal epithelium of surface and low epithelium of glands, with only very few mitoses in the surface epithelium; there were occasionally some small vacuoles in the epithelium. The connective tissue was edematous. The blood vessels contained many leucocytes and occasionally a mitosis can be seen in an endothelial cell. Here again the typical uterine changes are absent.

(7) No. 989. Six days, eighteen hours, after copulation excise one corpus luteum in left ovary, excise the entire right ovary without corpora lutea. Examination eleven days later showed one pregnancy in the left horn of the uterus and a young corpus luteum in the left ovary. The center of the corpus luteum was filled with loose connective tissue. There were small and small-medium sized good follicles and many follicles in a medium and late stage of connective tissue atresia. Rupture had taken place about three to four days previously (about fourteen to fifteen days after copulation). The right uterus showed cuboidal-cylindrical epithelium which at some places was somewhat higher. It contained some vacuoles with chromatic material and very few mitoses; the glands were cuboidal-cylindrical and without mitoses. The connective tissue is fibrillar, without mitoses. Cyclic changes are absent.

(8) No. 988. Five days, nineteen and a half hours after copulation excise one corpus luteum in right ovary and extirpate the whole left ovary with two corpora lutea. Examination ten days later. One pregnancy in right horn of uterus. In the right ovary there were young corpora lutea in which the central cavity had

been filled with connective tissue. There were present small and large good follicles. In a few large follicles there was just a beginning of granulosa degeneration. There were many follicles in a late stage of connective tissue degeneration. A new ovulation had taken place about six to seven days previously (eleven to twelve days after the previous copulation). The uterus on both sides showed the absence of a cell layer and of mitoses in the connective tissue which was fibrillar. The surface epithelium was cuboidal or cuboidal-cylindrical, and contained a number of mitoses. The glands showed low epithelium without mitoses.

(9) No. 979. Three days, four hours after copulation excise piece of right uterus. Six days, four hours after copulation excise one corpus luteum in right ovary, extirpate the whole left ovary (with two corpora lutea). Examination twelve days later showed three pregnancies in the left horn. In the right ovary three new corpora lutea had formed not quite three days previously, about fifteen and a half days after the previous copulation. The remaining uterus on the right side showed cuboidal or low cylindrical surface epithelium with a few vacuoles and some mitoses. The glands show cylindrical shape and are at some places higher and contain mitoses. At one place there is more cellular connective tissue with some mitoses in the connective tissue cells present. At this place there had evidently a cut been made at the time of the first operation and it is probable that the abnormality which we find here has been caused either through this cut, or perhaps through an ovum that began to penetrate here into the mucosa but did not continue to develop. However that may be, the changes which we find at one place in the mucosa do not correspond to the stage of the sexual cycle in which the animal was at the time.

(10) No. 987. Five days, nineteen hours after copulation, extirpate right ovary with two corpora lutea, excise one corpus luteum in the left ovary. Examination twelve days later showed two pregnancies in the right horn, apparently none in the left. But microscopic examination disclosed that at one place in the left horn, the ovum had also inserted itself, caused the production of a small decidua, but that the ovum had found difficulty in developing,—perhaps the decidual reaction being not strong

enough. In the left ovary, there were three new corpora lutea present, an ovulation having taken place approximately four to five days previously (thirteen to fourteen days after copulation). The uterus showed low cuboidal or low cylindrical surface epithelium with a few mitoses at some places, glands with cuboidal-cylindrical, not very high cells, without mitoses, fibrillar connective tissue in the mucosa without mitoses, with exception of one place where evidently the ovum had fixed itself and called forth the development of a small decidua with mitotic divisions in the small decidual cells. The typical cyclic changes of the uterus are therefore absent.

(11) No. 967. Three days, three and a half hours after copulation, excise two corpora lutea in the left and three corpora lutea in the right ovary. Examination fifteen days later showed one embryo and placenta in the right horn of the uterus. The left horn appeared thickened. In one ovary we found one, in the other three corpora lutea; their cavity is filled with connective tissue. There are already large good follicles formed, but no granulosa degeneration has as yet taken place. New ovulation occurred about six days previously (twelve and a half days after copulation). The uterus showed at various places the typical structure of the pregnant uterus without formation of a cell-layer. Cyclic changes did not take place in the uterus during pregnancy.

(12) No. 968. Three days, thirteen hours and a half after copulation excise three corpora lutea in the left and one corpus luteum in the right ovary. Examination eighteen and a half days after copulation showed three pregnancies in the right and one small one in the upper part of the left horn. In one ovary two new corpora lutea had been formed about seven or eight days previously (ten to eleven days after the previous copulation). The mucosa of the uterus presented the typical picture of a pregnant uterus.

(13) No. 866. Seven days after copulation excise several corpora lutea both in the left and right ovary. Examination eleven days later. Abortion was in progress in both horns of the uterus. A new ovulation had taken place in one of the ovaries about two to three days previously. The cavity of the

corpora lutea was partly filled by connective tissue. In the uterine mucosa processes of regeneration took place after abortion, polynuclear leucocytes migrated through the mucosa.

(14) No. 673. Four days, two and a half hours after copulation, one corpus luteum was excised in each ovary. At the examination fourteen days later one pregnancy was found in the right horn; in the left horn there was a dilated part. In the left ovary about three to four days previously two follicles had ruptured (fourteen to fifteen days after the previous copulation; new corpora lutea had formed). In the left uterus we found cuboidal to cylindrical epithelium of the surface without mitoses; some epithelium was raised by edematous fluid; the gland ducts were drawn out; the connective tissue cells in the mucosa showed many mitoses. It is possible that an abortion had taken place in the left horn of the uterus and that this complication may explain the cell proliferation in the connective tissue.

(15) No. 1219. Three days, nineteen hours after copulation, one corpus luteum was excised in each ovary. Examination ten days later showed two pregnancies in left, one in right horn of the uterus. In the ovaries we found good follicles of small to medium size, many follicles are in a condition of early or medium connective tissue atresia. In one ovary there is a young corpus luteum with a central cavity; some blood vessels begin to grow into the corpus luteum. Ovulation had taken place about one to two days previously (about twelve to thirteen days after copulation). In the uterus we find cuboidal or cuboidal-cylindrical surface epithelium in which there are vacuoles caused by immigrated cells. There are some rare mitoses in the surface epithelium. The epithelium of the glands is low cuboidal or cuboidal to cylindrical and is without mitoses. The connective tissue is fibrillar and contains small nuclei; no mitoses are present. The early pregnancy prevents the cyclic changes in the uterus.

We see, therefore, that during pregnancy the typical cyclic changes as we described them above do not take place. Instead we find on the whole the characteristic structure of the pregnant uterus. There are two or three specimens in which some doubt about the interpretation of the structural condition of the uterus

might arise. It is probable that in those cases secondary changes, due to embedding of an ovum which was not followed by normal embryonic development, had taken place in the mucosa. Only in one case there might be some doubt as to whether the typical cyclic changes had not taken place in the uterus notwithstanding the presence of pregnancy.

As to the way in which pregnancy influences the uterine mucosa, it is probable that the activity of the living decidual cells prevents the proliferation of the uterine mucosa. It cannot be a mechanical effect of pull on the uterine wall though the ovisac because the uterus of a nonpregnant horn behaves in a similar manner as the pregnant horn. If ovulation takes place after an experimentally produced placentoma has become necrotic the typical cyclic changes of the uterus follow ovulation, as in the following experiments:

No. 1152. Six days, twenty and one half hours after copulation, cuts were made into the uterine wall; examination nineteen days later (twenty-five days, twenty and a half hours after copulation). In the ovaries we found just ruptured follicles. There were present corpora lutea which were beginning to become vacuolar and to shrink (the corpora lutea of the former generation). Small good follicles as well as follicles with granulosa degeneration into which connective tissue began to grow were seen. These conditions indicated that ovulation had taken place within the previous twenty-four hours. The left uterus above the necrotic placentoma showed high cylindrical epithelium with a hyaline basal area. At some places the epithelium is lower as a result of pressure. The glands have high or medium cylindrical epithelium. There are some dilated gland ducts filled with polynuclear leucocytes. No mitoses are present in the surface epithelium and only a few in the gland ducts. At some places polynuclear leucocytes migrate into the surface epithelium and disintegrate into small chromatin particles. The structure of the uterus corresponds therefore to the condition found approximately within the first thirty-six hours after ovulation. The condition of the ovaries and of the uterus correspond to each other.

Also in another guinea-pig (No. 1140) the presence of necrotic placentomata in both horns of the uterus did not prevent the

development of the typical cyclic changes in the uterus. In this case cuts had been made into both horns of the uterus six days, six and a half hours after copulation. Nineteen days later, twenty-five days, eight and a half hours after copulation, we find on examination the presence of necrotic placentomata. Some small areas of the placentoma were still alive. Condition of the ovaries showed that ovulation had taken place about five days previously. Correspondingly we find in the uterine mucosa a cell layer with mitoses in connective tissue cells and some mitoses in gland fundi. The surface epithelium is cuboidal to cylindrical and contains some mitoses, perhaps as a result of the regenerative changes which are taking place at that time.

Pregnancy seems also to prevent the changes in the uterus which accompany the period of heat. This we found in guinea-pig No. 1300 in which three days, eighteen hours after copulation the thyroids had been extirpated. Examination seventeen days, nineteen and a half hours after copulation showed that this did not interfere with the development of the typical cyclic changes in the ovaries. They present the picture characteristic of this period. There are present several fully matured follicles ready to rupture, but the corpora lutea of pregnancy which do not show any sign of vacuolization and have vessels with well developed walls, prevent this rupture. We should expect under those conditions (period of time, presence of mature follicles) in a non-pregnant uterus high cylindrical epithelium of the surface and of the gland ducts, lower gland fundi, the nuclei of the connective tissue somewhat large and vesicular. Instead, we find the typical picture of the uterus during pregnancy; low cuboidal epithelium of the surface with a few isolated mitoses, low glands without mitoses, fibrillar connective tissue with small nuclei. At some places transudate raises the surface epithelium from the underlying connective tissue. Is it not probable that extirpation of the thyroids prevents the uterine changes accompanying heat because we observed the occurrence of these changes in another guinea-pig in which the thyroid had been removed previously. We may, therefore, conclude that the presence of pregnancy prevents those changes in the uterus which accompany the period of heat. And it appears probable that pregnancy prevents also the psychical changes characteristic of the state of heat.

## V. THE INFLUENCE OF EXTIRPATION OF THE CORPORA LUTEA ON THE DURATION OF THE CYCLIC PERIOD.

I have previously shown that the duration of the sexual period in the mammalian female depends upon the duration of life of the corpus luteum.<sup>1</sup> The corpus luteum prevents a new ovulation and the onset of a new sexual cycle.

In our former experiments some operative interference had usually taken place in the case of the control guinea-pigs as well as in those in which the corpora lutea had been excised. It was therefore necessary to determine the length of the sexual cycle in the normal guinea-pig. This can be done by observing the time of the heat of a guinea-pig and by examining uterus and ovaries at known intervals. Under those conditions we found the length of the sexual period to be usually sixteen to eighteen or nineteen days; sometimes the new ovulation may take place as early as fifteen days after copulation. In two exceptional cases we observed the new ovulation as early as thirteen and a half to fourteen and a half days. If we allow copulation to take place and ligature the tubes at their juncture with the uterus, and in addition, the upper part of the uterus, within the first two and a half days after copulation, the new ovulation also may take place between the sixteenth and eighteenth day, but in other cases it occurs later. If we make incisions into the uterus throughout its whole length five to seven days after copulation, ovulation takes place in the majority of cases between the twentieth and thirtieth day after copulation. At the times ovulation occurs the corpora lutea of the previous sexual period have begun to degenerate and the experimentally produced placentomata have to a great extent become necrotic. The beginning degeneration of the corpora lutea is a prerequisite for the new ovulation. If, after copulation, pregnancy is permitted to take its normal course, no ovulation occurs until birth has taken place. If abortion has taken place, a new ovulation also can occur.

If we excise the corpora lutea within the first week after copulation, a new ovulation occurs in the majority of cases

<sup>1</sup> *Zentralblatt f. Physiologie*, Bd. XXIII., No. 3, *Deutsche Med. Wochenschrift*, 1911, No. 1.



between the tenth and fifteenth day after copulation. We observed it as early as eight and a half and nine days after copulation. Pregnancy does not prevent the early ovulation after a complete extirpation of the corpora lutea. It is only the persistence of the corpora lutea of pregnancy which prevents the ovulation. Pregnancy however prevents, as we saw, the cyclic changes in the uterus which accompany and follow ovulation. On a former occasion I suggested that embryonic structures determine the persistence of the corpora lutea during pregnancy.<sup>1</sup> We are at the present time testing this hypothesis experimentally.<sup>2</sup> If we extirpate the corpora lutea incompletely, no new ovulation takes place.

These experiments, as well as those mentioned above which have already been partly published, and which as far as they concern new problems shall be published more in detail in the near future, clear up to a great extent the mechanism of the sexual cycle.

## VI. THE SIGNS OF HEAT IN THE GUINEA-PIG.<sup>3</sup>

(Report by Miss A. E. C. Lathrop.)<sup>4</sup>

"When a number of females are kept together in a large pen,

<sup>1</sup> *Zentralblatt f. Physiologie*, Bd. XXIV., No. 6.

<sup>2</sup> We produced recently experimentally an early stage of extrauterine pregnancy in a guinea-pig. The presence of some living embryonic structures and of fetal placenta did not prevent the degeneration of corpora lutea and the subsequent rupture of follicles. On the other hand the corpora lutea persisted as long as experimentally produced placentomata (structures of maternal origin) remained alive in cases in which we made incisions into the uterus six or seven days after copulation. In some of these cases fetal structures developed in these placentomata; in other cases no fetal structures could be found. It is therefore possible that the maternal placenta determines directly the life of the corpora lutea and that the embryonic structures act only indirectly by prolonging the life of the placentomata. We are testing experimentally this theory at the present time.

<sup>3</sup> The condition of heat in the majority of the guinea-pigs which we used was observed by the breeders, Mr. J. M. Simpson in Colwyn, Pa., and Miss A. E. C. Lathrop in Granby, Mass. Dr. O. Ishii also observed the condition of heat in a number of cases. I had an opportunity to control the correctness of these observations by the microscopic examination of ovaries and uterus. In almost all cases I found the observations of the breeders confirmed by the microscopical examination.

<sup>4</sup> I asked Miss A. E. C. Lathrop to observe the signs of heat in the guinea-pig and she sent a statement of her observations which, with her permission, I wish to incorporate in my paper after some slight changes have been made. She writes as above.

some will be seen sitting quietly, some eating a little, or walking about, making a small, sociable clucking noise.

"If one moves occasionally, rather majestically, among the rest, making a low, purring noise, similar to the noise of the male, she is probably in heat; if not, she soon will be. In some cases, a female guinea-pig may reach a state of excitement in which she assumes the manners of a male and attempts copulation with another guinea-pig which happens to be in heat. She, as well as the second guinea-pig that allows her to attempt the rôle of a male, will almost always be found ready for copulation.

"In many other cases, however, no such clear indications are present, but on close observation it will be seen that some female which is sitting quietly will be found to elevate slightly her hips whenever another guinea-pig happens to touch her. Again other females will show no sign of their condition, unless an active male is put among them. Those in heat take interest in the male, when he comes near them, while those not in heat or near the period of heat will kick him and hop away, making a little complaining noise when he pays attention to them. The male has no means of selecting the females which are in heat. When he has accidentally found one, he cannot find her again a moment later, but must try every female which he happens to come near to until he by chance meets again the animal in heat. Neither do the females that are in heat go to the male, but they wait, wherever they happen to be, until he comes to them. Some females will not give any indications whatever of their condition, but only when the male attempts copulation will they be found to be in heat.

"There are occasionally individuals which always appear to be in heat; at frequent intervals when not busy eating they purr and walk about like a male, but never seem to be actually ready for copulation. They resent the advances of the male at all times and yet are not sterile; when left for some months in a lot of males and females they may become pregnant.

"When one or very few females are kept in a small cage and have become relatively tame, those in heat when tickled along flanks and hips will react to the touch of the fingers, assuming a

position suitable for copulation.<sup>1</sup> This sign is, however, of no use when the animals are timid or when a number of the females are kept in the pen; under those conditions they pile up in a corner when one tries to touch them.

"The condition of the vulva may be of value in determining the state of the female. If a drop of mucus can be seen in the vulva, the animal is not in heat, even if acting somewhat excitedly, but it will be found in heat within a few hours. At the times of heat we find usually a little moisture or almost dried mucus at the vulva and a slight enlargement or swelling of the entrance to the vagina which may be so slight that it becomes noticeable only if the animal is compared with others.

"In some, perhaps in most cases, a day or two before heat the animal while not showing any of the above-mentioned signs, may be unusually lively and playful, and when taken in hand and brushed very lightly over pelvic region, we notice a twitching about the pelvis and especially the vulva."

## VII. EFFECT OF EXTIRPATION OF THE OVARIES ON THE CYCLIC CHANGES IN THE UTERUS.

We found that extirpation of the corpora lutea shortens the sexual cycle. It does not to any noticeable extent influence the various stages in the development of the ovarian follicles, but it causes an early rupture of mature follicles. Extirpation of the corpora lutea changes however the cyclic changes in the uterus. It prevents the predecidual proliferation of the connective tissue cells of the mucosa and modifies also to some extent the cyclic changes in the uterine epithelium. It does not however prevent those changes in the uterus which accompany heat and precede ovulation. The existence of a corpus luteum is required only as far as a certain part of the cyclic changes in the uterus is concerned; certain other changes (those preceding ovulation) are in all probability in a similar manner as ovulation itself inhibited by the existence of a functioning corpus luteum. However, if we extirpate both ovaries instead of the corpora lutea, all cyclic changes in the uterus come to a standstill.

<sup>1</sup> A similar observation had been previously communicated to me by Mr. J. M. Simpson.

Several months after castration, the wall of the uterus is thin; the surface epithelium is cuboidal or low cylindrical. There are mitoses present in the surface epithelium; their number varies. The glands are small and without mitoses; the connective tissue of the mucosa is fibrillar, contains small nuclei and is somewhat richer in nuclei directly beneath the epithelium than in the deeper parts of the mucosa. Two to three weeks after castration we find also low cuboidal or low cylindrical epithelium covering the mucosa of the uterus; no mitoses are present in the gland cells which are all small. The connective tissue is fibrillar and the connective tissue nuclei are small and without mitoses.

We see that after total extirpation of the ovaries the mucosa of the uterus becomes similar to the mucosa of the pregnant uterus in a non-pregnant horn. Gradually all the layers of the uterine wall seem to become thinner.

If we extirpate the ovaries within the first twenty-four hours after copulation and examine the uterine mucosa six or seven days after copulation we find the surface epithelium usually low cuboidal or cylindrical; it may, however, be somewhat higher; there are mitoses present in the surface epithelium; the glands have low epithelium and are usually without mitoses. In the connective tissue no cell-layer developed and no mitoses are visible. We find, therefore, here a similar result as after extirpation of the corpora lutea, namely, inhibition of the connective tissue proliferation and at the same time continued mitotic proliferation in the surface epithelium, which is lacking at this period in the normal uterine cycle. The extirpation of the ovaries acts in this respect principally through the lack of the corpora lutea which castration entails. In one case, however, in which fresh corpora lutea of the guinea-pigs were injected into a guinea-pig which had been castrated sixteen and a half hours after copulation, five days after castration a few mitoses were found in the connective tissue of the mucosa. We must leave it at present undecided whether the injection of the corpus luteum substance produced this result.

If we extirpate within the first twenty-four hours following copulation the ovaries and make incisions into the uterus six to seven days after copulation we find on examination ten days

after the last operation the absence of placentomata in the uterus. Mitoses are, however, present in the surface epithelium and sometimes also in the gland cells. Twice we found a few mitoses in the connective tissue of the mucosa which may either be myxoid in character or show the usual fibrillar character. Just as early extirpation of the corpora lutea prevents the experimental placentomata, so does extirpation of the ovaries have the same effect and we may, therefore, assume that also in this case extirpation of the ovaries is effective through the accompanying removal of the corpora lutea.

Through lack of the corpora lutea the sensitizing or preparing substance is removed which in combination with the mechanical factors causes the predecidual cell proliferation and the development of the placentomata. Under these conditions the cuts do not cause proliferation in the connective tissue of the mucosa.

If we extirpate the ovaries six to seven days after copulation and at the same time make incisions into the uterus, we may find on examination ten to thirteen days later either none (two cases), or very small placentomata (in one case in which the examination had been made thirteen days after excising the uterus). In the last mentioned case, about one half of the placentoma had become necrotic, the remaining part showed a hyaline character with nuclei embedded in a homogeneous glassy matrix. At one place there were still visible in the placentoma parts of the fetal placenta in the form of syncytiomatous vessels passing into the maternal tissue and also in the surrounding fat tissue. The extirpation of the ovaries caused in this case a very incomplete and retarded development of the ovum; a similar retardation in the development of the ovum we found also in a case of extrauterine pregnancy and a similar effect may be observed after extirpation of the corpora lutea. Under these conditions the soil is evidently not favorable for the development of the ovum.

In three cases in which the ovaries were extirpated eight days or almost eight days after copulation and at the same time incisions were made into the uterus, very small placentomata developed in two cases and only a trace of a placentoma in one case. On examination eleven days after the operation, a partial

necrosis was found in the placentoma; no mitoses, or only exceptional mitoses were found. Under certain conditions we observed however in the placentoma an amitotic proliferation of nuclei which may lead to the formation of giant cells. The living parts of the placentomata were hyaline and partly vacuolar.

Extirpation of the ovaries six to eight days after copulation does not prevent, therefore, entirely the production of placentomata through incisions made into the uterus simultaneously with the castration, but it reduces very much the cell proliferation and may cause a partial early necrosis.

We found also that extirpation of the corpora lutea six to eight days after copulation led to the production of placentomata which were smaller than usual. It is however possible that extirpation of the ovaries has a still more strongly inhibiting action on the growth of the placentomata than removal of the corpora lutea.

In several other series of experiments the ovaries were extirpated at periods following the incisions into the uterus. If the incisions into the uterus were made about six days after copulation, the ovaries extirpated two days later and the examination made eight or ten days after the last operation, placentomata developed in all cases, but their size varied. In one case they were of medium size, but usually they were smaller than normal. The amount of necrosis and hemorrhage also varied; these changes could be very insignificant or they could be very considerable.

In another series incisions were made into the uterus about six days after copulation; seven days later the ovaries were extirpated and seven days after castration the examination was made. In these experiments the placentomata were therefore fourteen days old at the time of examination, and the ovaries were extirpated at a time when the placentomata had already formed. The placentomata were found almost entirely necrotic; some small living areas were present usually directly under the outer surface of the placentoma or near the mucosa,—both places where the nourishment was still better. No mitoses were seen in the living part of the placentoma.

In the surface epithelium of the mucosa and in the glands of the

uterus mitoses were found. In one case mitoses were also found in the myxoid connective tissue of the mucosa and in this case mitoses in the glands were usually present at places in the neighborhood where also the connective tissue showed mitoses. In other cases, however, mitoses were only found in the surface epithelium and glands, but not in the connective tissue. These changes in the mucosa are in all probability to be interpreted as regenerative in character, following the necrosis of the placentoma.

We may, therefore, conclude that extirpation of the ovaries does not prevent regenerative proliferation in the mucosa of the uterus; furthermore that extirpation of the ovaries shortens in all probability the life of the placentomata.

In a further series incisions were made into the uterus six to seven days after copulation; ten days later the ovaries were extirpated, and after a further lapse of five days (fifteen days after incising the uterus) the examination was made. In these cases the ovaries were therefore extirpated at a still later period and the examination was made at a somewhat earlier date after castration. The placentomata were found to a great extent necrotic; some smaller parts which were better nourished, near the mucosa and around large blood vessels were usually still alive; no mitoses were found in the living cells. Here again we find proliferative processes in the surface epithelium and in three out of five cases also in the gland ducts of the uterine mucosa near the necrotic placentomata. The gland cells in those ducts in which mitoses are found are higher. Even in the connective tissue of the mucosa there may be a few mitoses in the connective tissue cells or in the blood vessels. This mitotic proliferation must in all probability again be interpreted as regenerative in character. Castration does therefore not prevent these regenerative changes in the mucosa of the uterus.

In control experiments in which incisions were made into the uterus six to eight days after copulation but in which the ovaries were left intact, the placentomata were still alive thirteen days, and in some cases partly alive eighteen and nineteen days after the incisions had been made. In other cases they were entirely necrotic eighteen to twenty-four days after incising the uterus.

If, however, only one horn of the uterus had been incised and pregnancy proceeded in the other horn the placentomata were invariably found alive even as late as twenty-five days after incising the uterus.

We see that the function of the ovaries depends partly upon the presence of functioning corpora lutea; the latter cause the predecidual proliferation of the connective tissue of the uterine mucosa, are a necessary factor for the production of the placentomata and determine directly or indirectly at certain periods of the sexual cycle, the size, shape and mitotic proliferation of the epithelial cells of the uterine mucosa. Other parts of the changes in the uterine mucosa, namely, those accompanying or directly preceding heat are determined by other parts of the ovaries and not by the corpora lutea. They take place after extirpation of the corpora lutea; they lead indeed to the formation of new corpora lutea; they are however prevented through the extirpation of the ovaries. Which part of the ovaries is responsible for these changes characteristic of heat cannot be easily determined experimentally but can only be surmised. On a former occasion we stated the reasons why we thought it very improbable that the so-called interstitial gland of the ovary is responsible for the cyclic changes accompanying heat.<sup>1</sup> In the first place in the ovary of the guinea-pig there does not exist a structure deserving of the name "interstitial gland." We merely find small shrinking connective tissue cells of theca interna filling the place of lost parts of the follicles which are in process of atresia; secondly the quantity of follicles in late stages of atresia is perhaps greater five to six days after ovulation than at the period of heat, There is usually towards the end of a cyclic period a considerable number of such follicles present in the ovary, but in other cases, especially in younger animals, the number present may be relatively small.

The only structure which is, so far as we know, invariably connected with the presence of heat and which originates at the time preceding heat is the mature follicle. The granulosa cells of a mature follicle differ in some of its morphological and physiological characteristics from those of ordinary growing follicles.<sup>2</sup>

<sup>1</sup> *Centralblatt f. Physiologie*, Bd. XXV., No. 9.

<sup>2</sup> *Journal of Morphology*, Vol. 22, March, 1911; *Virchows Arch.*, Bd. 206, 1911.



It is therefore probable that they are in some way responsible for the changes in the uterine mucosa accompanying heat. Even if extirpation of these follicles should not prevent the occurrence of heat, this would not be conclusive evidence against this assumption inasmuch as the mature follicles had already had an opportunity at the time of extirpation to exert their influence. In a similar manner we have shown previously that extirpation of the corpora lutea five to six days after ovulation does not prevent the production of placentomata, while extirpation done one day after ovulation has a preventive effect. There still remains of course the ordinary follicles as the possible source of the energy leading to these changes in the uterine mucosa; inasmuch as they are present equally at other times of the sexual cycle, while the mature follicles are present only at certain periods and especially at the time of heat or immediately preceding heat, it is more probable that the mature follicles are responsible for these changes. Whatever the part of the ovary may be that brings about these changes, there must be added to this positive factor two negative ones, namely the absence of a fully functioning corpus luteum and of pregnancy, these conditions being necessary for the development of the normal and complete sexual cycle.

As we saw, the ovaries have still another function, namely that of maintaining the full size of the uterus. After castration various constituent parts of the uterine wall diminish in size.

### VIII. SUMMARY.

1. The cyclic changes in the epithelial as well as connective tissue structures of the uterus during heat preceding copulation and the changes following copulation are described; the influence of polynuclear leucocytes in these changes is shown. The latter are present during the first two days following copulation. The decidual cells originate from the connective tissue cells of the mucosa.

Various periods of the sexual cycle are characterized through the shape and mitotic proliferation of various epithelial and of the connective tissue cells. From the sixth to the twelfth day after ovulation mitoses are usually absent in the epithelial

structures; afterwards they begin to reappear, from the eighth day on to the end of the sexual cycle mitoses are absent in the connective tissue.

2. As long as the corpora lutea functionate, the presence of mature follicles in the ovaries does not produce those changes in the uterine mucosa which are characteristic of the period of heat.

3. During pregnancy the structure of the uterus is that of a resting organ, in which epithelial as well as connective tissue cells are small and the latter are without mitotic proliferation.

4. In animals in which heat has been observed without copulation taking place, the cyclic changes in the uterus are approximately the same as in animals in which copulation did take place, in which however pregnancy had been prevented through an early ligature of the fallopian tubes. The main difference in these two series is caused through the very marked migration of polynuclear leucocytes through the mucosa in cases in which copulation took place.

5. Ovulation is usually accompanied or directly followed by certain changes in the uterine mucosa. These changes permit us in many cases to decide whether or not in an animal in the period of heat ovulation has or has not yet taken place.

6. Extirpation of almost the whole uterus or thyroids does not prevent the occurrence of heat in the operated animals.

7. In animals which were prevented from copulating or in which the fallopian tubes were ligated soon after copulation, the period of heat occurs approximately every fifteen to nineteen days.

8. The proportion of ovarian follicles which are in the late stages of connective tissue atresia to well preserved follicles and follicles in the stage of granulosa degeneration shows two maxima, one about six to seven days after ovulation and another at the time preceding the next ovulation. Under certain conditions, however, the number of quite atretic follicles may be small at the time of heat, namely in young guinea-pigs which are in heat for the first time, and it may be relatively large at other periods of the sexual cycle in old guinea-pigs.

9. As we showed previously an early extirpation of the corpora

lutea leads in the large majority of cases to an acceleration of the next ovulation. Certain conditions, however, may prevent the early ovulation. In the latter cases the structure of the uterus corresponds to the late stage of the sexual cycle. If however a new premature ovulation is brought about through the extirpation of the corpora lutea, a new cycle starts in the uterus at the time of the accelerated ovulation. Mature follicles, or possibly other follicles, are in the absence of corpora lutea able to call forth the structural changes in the uterus accompanying heat and the rupture of the follicles and development of corpora lutea is followed by the typical uterine cyclic changes.

10. We stated previously that also during pregnancy extirpation of the corpora lutea is followed by an early ovulation. While thus pregnancy in itself does not prevent an ovulation to take place (only the corpora lutea persisting during pregnancy preventing the ovulation) pregnancy does prevent the cyclic changes of the uterus preceding, accompanying or following ovulation; during pregnancy the uterus retains its resting condition notwithstanding ovulation. This influence of pregnancy is not a mechanical one, inasmuch as it is found in the non-pregnant horn as well as in the pregnant horn in cases in which a pregnancy developed only in one horn. The presence of a necrotic placentoma or the occurrence of an abortion does not prevent the cyclic changes in the uterus that set in with ovulation.

11. If five to seven days after copulation both horns of the uterus are split lengthwise and the development of a normal pregnancy is prevented, ovulation is delayed under those conditions; it occurs between the twentieth and thirtieth day after the previous copulation, even in cases in which a developing embryo could not be seen in the placentomata growing at the site of the incisions. On the other hand in a case of an experimentally produced extrauterine pregnancy degeneration of the corpus luteum and a new ovulation were not delayed notwithstanding the presence of living embryonic (including placental structures of embryonic origin) in the animal. These observations suggest that it is primarily the life of the maternal part of the placenta which prevents the new ovulation during pregnancy and that the embryonic structures are only indirectly concerned

in this effect. We are testing this suggestion still further at the present time.

12. A description of the signs of heat is given in accordance with the observations of the breeder, Miss A. E. C. Lathrop.

13. After total extirpation of the ovaries, the uterine mucosa becomes similar to the mucosa of the pregnant uterus in a non-pregnant horn; gradually an atrophy of the different layers of the uterine wall takes place. If we extirpate the ovaries soon after ovulation the effect is the same as if the corpora lutea are extirpated at that period, as far as the predecidual proliferation in the connective tissue and the accompanying changes in the epithelium which take place between the fourth and seventh day are concerned. As far as this effect is concerned the corpus luteum is the active part of the ovaries. While, however, extirpation of the corpora lutea does not prevent those uterine changes which accompany heat and does not prevent a new sexual cycle, extirpation of the ovaries prevents all cyclic changes in the uterus.

14. Early extirpation of the corpora lutea within the first forty hours after copulation prevents in a similar manner the development of experimental placentomata as an early extirpation of the ovaries. If the ovaries are removed six to eight days after copulation and at the same time incisions are made into the uterus, either none, or only very small placentomata develop and the developing placentomata die at an earlier date than they would have done otherwise. An extirpation of the corpora lutea six to seven days after copulation also causes the developing placentomata to be smaller. If under these conditions an ovum develops in the incised uterus within the decidual tissue, the development of the ovum is usually much retarded. A similar retardation of the development of the ovum we observed in a case of experimentally produced extrauterine pregnancy in the guinea-pig. If the ovaries are extirpated two days after the making of the incisions the developing placentomata are usually smaller. Castration done at a time when the placentomata had already reached a considerable size causes an acceleration in the necrosis of the placentomata. Castration does however not prevent regenerative changes in the uterine mucosa.

15. The existence of pregnancy in one horn of the uterus prolongs markedly the life of placentomata produced in the other horn.

16. For certain phases of the cyclic changes of the uterus the presence, for other phases the absence, of a functioning corpus luteum is necessary; but certain other ovarian structures (probably mature follicles and not the so-called interstitial gland) are required for the latter phases. In addition the absence of pregnancy (and probably of living placentomata) is a condition for the typical course of the cyclic changes in the uterine mucosa.